



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Earl et al**

Application No: **10/612,014**

Group Art Unit: **1625**

Filed: **July 3, 2003**

Examiner: **E. Huang**

For: **Nitrosated Nonsteroidal Antiinflammatory Compounds, Compositions and Methods of Uses**

Attorney Docket No: **102258.156 US1**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

**Provisional Response to Restriction Requirement and
Request for Reconsideration of Restriction Requirement Under 37 C.F.R. § 1.143**

I. Introductory Comments

This response is submitted in reply to the Restriction Requirement dated September 3, 2004, for which a response is due on or before November 3, 2004.

The Commissioner is authorized to charge the one month extension of time fee of \$55 to Deposit Account No. 08-0219; and charge any other necessary fees to Deposit Account No. 08-0219 to maintain the pendency of the present application.

II. Request for Reconsideration of Restriction Requirement

Under 37 C.F.R. § 1.143, Applicants respectfully request reconsideration of the restriction requirement dated May 27, 2004.

The examiner restricted the invention as follows:

Group I	Claims 1-4, 55, 56 in part	Compound of Formula I wherein R _n is a theinyl of Formula 1 or 10
Group II	Claims 1-4, 55, 56 in part	Compound of Formula I wherein R _n is a keto group Formula 2, 22, 27 or 38
Group III	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an isoindoyl of Formula 3

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Group IV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a heterocyclic tricyclic group of Formula 4 or 51
Group V	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a pyrrolyl of Formula 5, 29, 33 or 45
Group VI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a S(O) _s containing group of Formula 6
Group VII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a halo containing group Formula 7
Group VIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a indolyl Formula 8, 23 or 24
Group IX	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a carboxzoyl of Formula 9 or 28
Group X	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an ether containing group of Formula 11, 12 or 19
Group XI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an imidazopyridine of Formula 13
Group XII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a 1,3 oxazolyl of Formula 12 ¹ , 39 or 49
Group XIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a hydrocarbyl of Formula 15 or 35
Group XIV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an amine containing group of Formula 16, 20, 25 or 27 ²
Group XV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a carboxylic ester containing group of Formula 18
Group XVI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a benzoxazolyl of Formula 21 or 42
Group XVII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a benzopyrazolyl of Formula 26
Group XVIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a pyrrolyl of Formula 29, 33 or 45 ³

¹ Applicants assume this is a typographically error and that the Examiner meant to refer to the compound of Formula 14.

² Applicants assume this is a typographically error as the compound of Formula 27 is already assigned to Group II

³ Applicants assume this is a typographically error as the compound of Formula 29, 33 and 45 are already assigned to Group V

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Group XIX	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a pyrazolyl of Formula 30, 31, 40 or 47
Group XX	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a phenothiazinyl of Formula 4 or 51 ⁴
Group XXI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a pyrrolyl of Formula 32 or 43
Group XXII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a benzopyranylpiperidinyl of Formula 34
Group XXIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an oxygen containing tricyclic ring of Formula 36 or 37
Group XXIV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a 1,2 thiazolyl of Formula 41 or 46
Group XXV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is a sulfur containing tricyclic ring of Formula 44
Group XXVI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an amido containing group of Formula 48
Group XXVII ⁵	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R _n is an NOH containing moiety of Formula 50
Group XXVIII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is an amino containing group of Formula 1, 2, 9, 12, 15, 18 or 19
Group XXIX	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a hydroxy containing group of Formula 3, 4, or 11
Group XXX	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a carboxy ester containing group of Formula 5, 6, or 17
Group XXXI	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a nitrogen containing bicyclic group of Formula 7
Group XXXII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a benzoindolyl of Formula 8
Group XXXIII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a pyridinyl of Formula 10 or 16

⁴ Applicants assume this is a typographical error as the compound of Formula 41 and 51 are already assigned to Group IV

⁵ Applicants note that the compound of Formula I of Formulas 14 and 17 have not been assigned to any Group.

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Group XXXIV	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a indolyl of Formula 13
Group XXXV	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R _n is a chloro containing group of Formula 14
Group XXXVI	Claim 5	Method of treating or reducing inflammation, pain or fever using the compounds of Formula I or II
Group XXXVII	Claims 6, 7	Method for treating a gastrointestinal disorder using the compounds of Formula I or II
Group XXXVIII	Claims 8, 9	Method of treating for facilitating wound healing using the compounds of Formula I or II
Group XXXIX	Claim 10	Method of treating or reversing gastrointestinal, renal and/or respiratory using the compounds of Formula I or II
Group XL	Claims 11-14	Method of treating for an inflammatory disease using the compounds of Formula I or II
Group XLI	Claim 15	Method of treating for an ophthalmic disorder using the compounds of Formula I or II
Group XLII	Claims 16, 17	Compositions comprising the compounds of Formula I or II of claim 1 and at least one additional therapeutic agent
Group XLIII	Claim 18	Method of treating or reducing inflammation, pain or fever using the composition of claim 16
Group XLIV	Claims 19, 20	Method for treating a gastrointestinal disorder using the composition of claim 16
Group XLV	Claims 21, 22	Method for facilitating wound healing using the composition of claim 16
Group XLVI	Claim 23	Method of treating or reversing gastrointestinal, renal and/or respiratory toxicity using the composition of claim 16
Group XLVII	Claims 24-27	Method for treating an inflammatory disease using the composition of claim 16
Group XLVIII	Claim 28	Method for treating an ophthalmic disorder using the composition of claim 16
Group XLIX	Claims 29-37	Compositions comprising the compounds of Formula I or II of claim 1 and at least one nitric oxide donor compound

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Group L	Claims 38, 39, 58	Compositions comprising the compounds of claim 29 and at least one therapeutic agent
Group LI	Claim 40	Method of treating or reducing inflammation, pain or fever using the compositions of claim 29 or 38
Group LII	Claims 41, 42	Method for treating a gastrointestinal disorder using the composition of claim 29 or 38
Group LIII	Claims 43, 44	Method for facilitating wound healing using the composition of claim 29 or 38
Group LIV	Claim 45	Method of treating or reversing gastrointestinal, renal and/or respiratory toxicity using the composition of claim 29 or 38
Group LV	Claims 46-49	Method for treating an inflammatory disease using the composition of claim 29 or 38
Group LVI	Claim 50	Method for treating an ophthalmic disorder using the composition of claim 29 or 38
Group LVII	Claims 51-54, 58	Kits comprising the compound of claim 1 or 55, or a composition thereof with additional active ingredients

The claims in the pending application are directed to **nitrosated nonsteroidal antiinflammatory compounds**, and compositions comprising nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, and the methods of use for the compounds and/or compositions.

III. Restriction is Not Proper When the Claims are Related

As stated in MPEP §808.02, “[w]here, as disclosed in the application, the several inventions claimed are related, and such related inventions are not patentably distinct as claimed, restriction under 35 U. S. C. §121 is never proper (MPEP §806.05).”

All the pending claims are related. Thus, the restriction requirement is not proper. To show that the inventions are distinct, the Examiner must show either that (1) there is a separate classification of the claims; (2) a separate status in the art when they are classifiable together; or (3) a different field of search. *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

None of these three criteria have been shown with the claims of this application:

If the nitrosated nonsteroidal antiinflammatory compounds are allowable, then all the compositions requiring a nitrosated nonsteroidal antiinflammatory compounds would also be allowable and all the methods of use for these compositions would also be allowable. In other words, every pending claim that requires a **nitrosated nonsteroidal antiinflammatory compound** would also be allowable. *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

A search of the prior art for the nitrosated nonsteroidal antiinflammatory compounds would necessarily encompass a search of the prior art for the compositions for the nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, and their methods of use. Thus, the prior art for the nitrosated nonsteroidal antiinflammatory compounds of Groups I–XXVII of Formula I or Groups XXVII to XXXV of Formula II respectively, will also be the same prior art for the compositions, methods of use and kits for the nitrosated nonsteroidal antiinflammatory compounds (i.e., Groups XLIX – L or Groups XXXVI to XLVIII and Groups LI to LVII or Group LXVII).

The claims in the pending application are generally directed to nitrosated nonsteroidal antiinflammatory compounds of Formula I or Formula II, and compositions comprising nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, and the methods of use for the compounds and/or compositions.

Additionally, applicants respectfully submit that the Patent Office has failed to properly follow the MPEP guidelines for unity of invention within a Markush group. MPEP §803.02 states (Emphasis added):

“Broadly unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility”

The Examiner failed to appreciate that the compounds of formulas (I) or (II) are recognized classes of chemical compounds (i.e., nonsteroidal anti-inflammatory compounds) and there is an expectation from the knowledge in the art that members of this class (i.e., nonsteroidal antiinflammatory compounds) will behave in the same way in the context of the claimed invention.

III. Proposed restriction requirement

Applicants respectfully propose the following restriction requirement:

Group I	Claims 1-58 (in part)	Compounds and compositions of nitrosated nonsteroidal antiinflammatory compounds of Formula I, and optionally other compounds, methods of use for the compounds and/or compositions.
Group II	Claims 1-58 (in part)	Compounds and compositions of nitrosated nonsteroidal antiinflammatory compounds of Formula II, and optionally other compounds, methods of use for the compounds and/or compositions.

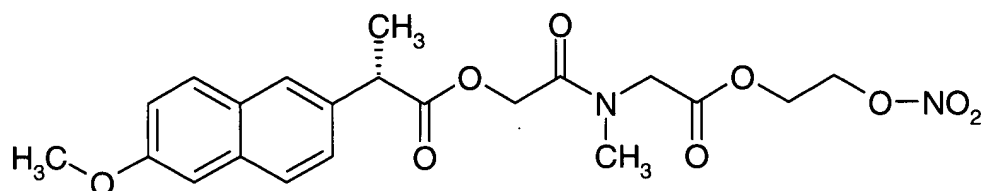
IV. Provisional Response to Restriction Requirement

Applicants provisionally elect Group X, claims 1-4, 55, 56 (in part) drawn to the compounds of Formula I, wherein R_n is an ether containing group of Formula 11, 12 or 19, with traverse.

V. Election of Species

In response to the election of species requirement, Applicants elect the nitrosated nonsteroidal antiinflammatory compound of Formula A, (N-methyl-N-(((2-(nitrooxy)ethyl)oxycarbonyl)methyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate, with traverse.

This compound has the structure:



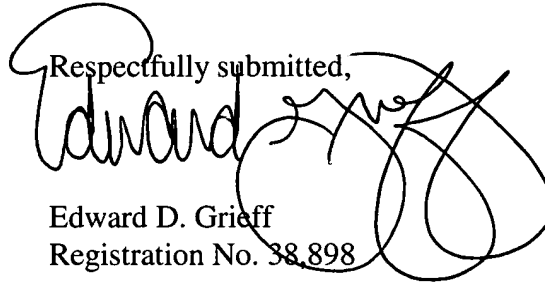
(A)

The synthesis of this compound is described in Example 20 of the specification at page 82, line 22 to page 84, line 21.

VI. Conclusion

Applicants respectfully request that the restriction requirement be withdrawn and be replaced with Applicant's proposed restriction requirement.

An early and favorable consideration and allowance of the pending claims is respectfully requested.

Respectfully submitted,

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